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EXAMINER	
LIU, SUE XU	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,684	WALDMAN, SCOTT A.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25-27,30-34,36,39,40,42-48,50-56 and 62-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25-27,30-34,36,39,40,42-48,50-56 and 62-67* is/are rejected.

7)☒ Claim(s) *67* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1-22, 24, 28, 29, 35, 37, 38, 41, 49 and 57-61 have been cancelled as filed 4/29/08.

Claims 67 has been added as filed 4/29/08.

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are currently pending.

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are being examined in this application.

Election/Restrictions

2. Applicant's election without traverse of Group I (claims 23-44), and species election of peptide having amino acid sequence of SEQ ID NO: 2 as the ST receptor binding ligand, and 5-fluorouracil as the species of active agent, in the reply entered, 02/01/05, is as previously acknowledged.

The newly added Claim 67 (as filed on 4/29/08) is grouped together with the elected Group I, and is examined in the instant application.

Priority

3. This application is a continuation of 09/263,477 (now abandoned), filed 3/5/99, which is a continuation of 08/583,447 (now US Patent 5,879,656), filed 1/5/96, which is a continuation-in-part of 08/141,892 (now US Patent 5,518,888), filed 10/26/93.

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 08/141,892, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The Grandparent patent application 08/141,892 (Now US Patent 5,518,888) does not appear to provide supports for the claimed invention regarding SEQ ID NO: 55 and 56, which are recited in Claims 25, 32, 43, 45, and 50 of the instant application.

Thus, the instant claims 25, 32, 43, 45, and 50 which recite sequences not disclosed in the parent applications are entitled only to the filing date of the application 08/583,447.

The filing date of the instant claimed invention of recited in Claims 25, 32, 43, 45, and 50 (in particular, SEQ ID Nos 55 and 56) is determined as the filing date of the US Application 08/583,447, **01/05/1996**.

Specification

4. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the **abstract not exceed 150 words** in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Applicants are also invited to update the continuing data (benefits claimed under 35 USC

119, 120, etc.) in the first line of the specification.

Claim Rejections Withdrawn

5. In light of applicants' amendments to the claims to correct the informalities of the claims, the objections to claims 23, 30 and 42 as set forth in the previous office action are withdrawn.

6. In light of applicants' amendments to the claims, the following claim rejections as set forth in the previous office action is withdrawn:

A.) Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Rejection

8. Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the pharmaceutical compositions in isolated cells, does not reasonably provide enablement for pharmaceutical uses in animals or humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The previous rejection over claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 is maintained for the reasons of record as set forth in the previous Office action. The previous rejection over claims 38, 41, 57 and 58 is moot due to applicant's cancellation of the said claims. The rejection over claim 67 is necessitated by applicant's amendment to the claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;

4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims

The instant claims recite a product of pharmaceutical composition comprising: a) ST receptor binding ligand; b) a non-peptide radiostable therapeutic (or active) agent; and, c) a pharmaceutical carrier or diluent wherein said ST receptor binding ligand is selected from the group consisting of: a peptide, an antibody and fragments thereof.

The breadth of the claims seems to encompass pharmaceutical composition comprising ST receptor binding ligands that can be peptides or antibodies, and non-peptide therapeutic (or active) agent with intended therapeutic uses in animals or humans for treatment of any disease. However, the instant specification does not describe using the claimed peptides as parts of pharmaceutical compositions to treat any disease. The instant specification only prophetically discussed the possibility of using the claimed peptides in combination with therapeutic (or active) agents as pharmaceutical composition to treat diseases such as cancer.

The nature of the invention

The nature of the invention as recited in the instant claims is pharmaceutical compositions with intended therapeutic uses to treat humans and/or other animals.

The state of the prior art/ The predictablility or lack thereof in the art

Utilization of peptides as pharmaceutical composition (especially administering to human) is highly unpredictable. In addition, treatments of various diseases (such as various cancers) using compositions comprising ST ligands and another agents are also highly unpredictable. There are many problems existing with the administration of peptide drugs to humans. First, the peptide drug may be toxic to the subject being administered, and hence will not elicit the intended pharmaceutical effects. To evaluate toxicity and efficacy of a peptide drug, pre-clinical animal model testing and clinical trials are required. Adverse effects of these peptide pharmaceuticals cannot be generalized, and are highly unpredictable. For example, Cianfrocca et al (British Journal of Cancer. (2006), pg 1-6; cited previously) have reported a phase I clinical trial on a particular peptide drug with only limited success in treating patients with cancer.

Second, the mode of delivery for these peptide drugs is also critical, and the success of the delivery is highly unpredictable. The major problem with peptide pharmaceuticals is the mode of delivery. For example, Russell-Jones reviews oral delivery of peptide and/or protein drugs (Journal of Drug Targeting. Vol. 12(2): 113-123. 2004; cited previously). The reference states that "peptide and protein pharmaceuticals, in contrast to the traditional chemically synthesized compounds, are highly susceptible to proteolysis within the intestine and also have very low oral bioavailabilities. The low oral bioavailability of these compounds is due to the almost impenetrable barrier provided by the epithelial cell layer to certain types of molecules…" (see pg 113, left col.) The reference also teaches non-oral dosage forms are more difficult and traumatic to self-administer than oral dosages. Although methods of enhancing the delivery of peptide drugs into subjects are in development, "early attempts to enhance the oral uptake of

many peptides and proteins were, in the main, unsuccessful" (see pg 121, left col., last para. of Russell-Jones reference).

Furthermore, the pharmaceutical conjugates claimed in the instant application may require delivery of the peptide drugs inside the cells to exert their pharmaceutical effects. This elicits additional problems such as specific cell targeting and cell penetration. El-Andaloussi et al (Current Pharmaceutical Design. Vol. 11: 3597-3611; 2005; cited previously), throughout the reference, review cell-penetrating peptides. The reference teaches that the "major obstacle in the development of new therapeutic agents is the low bioavailability of hydrophilic substances. Drugs that bind to intracellular targets must penetrate the lipid bilayer surrounding the cell in order to exert their effect" (see Abstract of the reference). The reference also teaches that cell-penetrating peptides are of special structure and properties (pg 3598 of the reference). The instant specification does not shown that the claimed peptides can penetrate cells, or demonstrating their specific cell-penetrating structures and/or properties.

In addition, the effects of compositions measured in *in vitro* testing (such as in cells) for treatment of diseases such as cancer cannot be reliably correlated to successful treatments in animals or humans. For example, Voskoglou-Nomiko et al (Clinical Cancer Research. Vol. 9: 4227-4239; 2003) teach no significant correlation observed between in vitro cell testing and clinical human data especially in colon cancer (e.g. pp. 4231-4232; Abstract; pp. 4235-4236, bridging). Both human and mouse xenografts (in vitro cell models) also did not provide reliable predictable model for clinical cancer analysis (e.g. Abstract). Thus, correlating in vitro cell data to human clinical outcome is highly unpredictable.

Therefore, the state of the art for using peptide pharmaceuticals to treat various diseases such as cancer or infectious disease is highly unpredictable. Although there are positive initial indications for the feasibility of using certain peptides for certain diseases in humans, there is no general demonstration of a successful treatment using peptides administered variously.

The level of one of ordinary skill

The level of skill would be high in order to carry out the intended use of the claimed pharmaceutical composition.

The amount of direction or guidance present / The presence or absence of working examples

The only examples of "pharmaceutical compositions" are the conjugates used to inhibit T84 cells in vitro in the instant specification at p. 72-75 (especially Example 6). The instant specification only recites that the tested cells (i.e. T84 cells) are incubated with the peptide-active agent conjugates, and then observing the inhibitory effect of the conjugates on the cells. There are no data indicating the peptide-conjugates' effects on any postulated diseases (such as cancer). No animal or human data are shown to indicate the pharmaceutical uses of the claimed peptides. That is no working examples are presented to demonstrate the pharmaceutical uses of the claimed peptides and their conjugates.

Where physiological activity is concerned (i.e., the claimed method of treatment), one skilled in the art reasonably would not and properly should not accept in vitro results as support for in vivo activity. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, Ltd., 927 F.2d 1200, 1216-1217, 18 USPQ2d 1016, 1030 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Therefore, to enable one

skilled in the art to use various compounds for treating any disease (including cancer) in vivo based solely on in vitro testing, as is the case here, some evidence correlating in vivo results to in vitro testing at the pertinent time is required. See *In re Brana*, 51 F.3d 1560, 1565 USPQ2d 1437, 1442 (Fed. Cir. 1995)

See also MPEP 2164.02:

"The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)" (emphasis added).

In this case, the instant specification does not provide any reasonable correlation between the *in vitro* compound assay with the *in vivo* treatment methods. As discussed supra, the state of the prior art does not provide reliable and/or predictable in vitro cell or animal models of various diseases (such as various cancers). Thus, the in vitro cell assays for determining pharmaceutical effects of various compositions do not constitute "working examples," because a predictable correlation between the in vitro assay and the in vivo utility has not been demonstrated either in the art or by the instant disclosure. Additionally, the in vitro data provided given the unpredictability of the art would not be viewed as correlative to human applications. In vivo application necessarily involves unpredictability with respect to physiological activity of an asserted process in humans. See discussion in Ex parte Kranz, 19 USPQ2d 1216,1218-1219 (6/90).

The quantity of experimentation needed

Due to the unpredictabilities of using peptides (and/or peptide conjugates) for treatment of various disease in any subject (as discussed supra), and the lack of guidance in the instant specification, undue experimentation would be required. Given the complications or mixed results of using peptides as pharmaceuticals to treat disease such as cancer, and the complexity in even developing a feasible peptide drug delivering method, undue experimentation would be required. Because the art does not provide successful and general methods of administering peptides for treatment of various diseases, undue experimentation such as trial-and-error process would have to be employed for developing the various components for peptide pharmaceuticals including the mode of delivery, dosage requirement, toxicity testing, efficacy testing, etc.

Conclusion

Due to the non-routine of experimentation necessary to determine the feasibility of using pharmaceutical composition comprising peptides for therapeutic uses; the lack of direction/guidance presented in the specification regarding the specific requirements for such a pharmaceutical composition; the unpredictability of the treatment methods using peptides as established by the state of the prior art; the breadth of the claims, undue experimentation would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the instant claimed invention is enabled in its full scope. (Reply, pp. 13+).

Contrary to applicants' assertion, the previously cited references provide ample evidence to demonstrate the "unpredictability" of using peptide or protein as pharmaceutical compositions. Applicants seem to argue that because some of the peptide drugs taught by the references (e.g. Cianfrocca et al) have limited effectiveness, peptide drugs, in general, are predictable and can be used as drugs. Although certain peptides (such as some of the peptides) taught by Cianfrocca reference have limited success, using peptides as drugs in general are highly unpredictable.

Because certain peptides as taught by Cianfrocca et al can be developed into successful drugs and other peptides cannot be developed into effective pharmaceutical compositions that indicate the high "unpredictability" of the art. There is nothing in the instant specification or prior art to structurally distinguish which peptides can or cannot be predictably developed into effective pharmaceutical compositions for treating various diseases. The question is "predictability" of the art for various peptide and/or peptide conjugate drugs, and it is not a question of whether peptides can or cannot be used as drugs. (see *In re Wands*, 8 USPQ2d 1400(1988)). As discussed previously, the Cianfrocca reference teaches drugs derived from peptides have been met with limited success and are highly unpredictable.

Applicant's arguments (Reply, p.14) regarding the difference between FDA standards and patentable difference is irrelevant. The question here is whether or not using "ST receptor binding ligands" as pharmaceutical compositions (i.e. as agents for treatment of various diseases) are enabled under 35 USC 112, 1st paragraph. The appropriate analysis under the "Wands factors" was conducted to indicate that the instant invention is not enabled, as discussed previously as well as supra.

The Russell-Jones reference demonstrates the high "unpredictability" of using peptide as pharmaceutical composition in the aspect of drug delivery (i.e. problems with administering to animals and/or human). As discussed previously, the reference also teaches non-oral dosage forms are more difficult and traumatic to self-administer than oral dosages (e.g. p.121), which also highlights the unpredictability of using peptides as drugs in various delivery forms.

Applicants also argue (Reply, p.15, para 2) that the instant invention does not have the "cell penetration" problem associated with peptide drugs that are discussed in the El-Andaloussi reference, because the instant claimed ligand bind to "a cell membrane protein" (i.e. the ST receptor). However, the instant specification does not specifically define the ST receptor is "a cell membrane protein" (see Definition for "ST receptor" on p. 6 of the instant spec.). As discussed above, the instant claimed invention is broad and encompassing pharmaceutical compositions for treatment of various diseases. The only examples of "pharmaceutical composition" are the conjugates used to inhibit T84 cells in vitro in the instant specification at p. 72-75 (especially Example 6). The instant specification does not disclose any pharmaceutical composition other than the conjugates used to inhibit the T84 cells. It is not clear if the delivery to T84 cells can be "reasonably correlated" to delivery to other types of cells, or cells within an

animal or human. It is also not shown that the claimed composition of "ST receptor" ligands can be used to treat any disease, for examples, such as cancer, AIDS, Alzheimer's diseases in any subject.

Applicants also argue the "Voskoglou-Nomiko" reference indicate the predictability of the state of the art (Reply, p.15-16). As discussed previously and above, the reference teaches no significant correlation observed between in vitro cell testing and clinical human data especially in colon cancer (e.g. pp. 4231-4232; Abstract; pp. 4235-4236, bridging). That is the correlation between in vitro result and in vivo effect is not well established and is unpredictable. Applicants pointed to the recitation on page 4227 of the reference that recites "the in vitro cell line and human xenograft models may be useful in predicting the Phage II clinical trial performance of cancer drugs" to indicate that the present invention is enabled. However, the recitation is only contemplating a possibility that the in vitro cell "may be" usefully and only if under the right circumstance. It does not conclusively state the in vitro data can be reliably correlated with in vivo pharmaceutical effects. Further, the statement of the reference is only in reference to "cancer drugs", which cannot be reasonably correlated to any disease or any composition.

Applicants also argue "One skilled in the art would expect that the peptide would have some level of activity in vivo." (Reply, p.14). However, as discussed previously, the case laws provide otherwise:

Where physiological activity is concerned (i.e., the claimed method of treatment), one skilled in the art reasonably would not and properly should not accept in vitro results as support for in vivo activity. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, Ltd., 927 F.2d 1200, 1216-1217, 18 USPQ2d 1016, 1030 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

In this case, applicants have not provide any data to shown a reasonable correlation between in vitro data and in vivo activity (such as art accepted animal model data). A mere allegation of expecting "some level of activity in vivo" is not sufficient to demonstrate predictability for in vivo treatments.

Thus, the previously cited references demonstrate "unpredictability" of various aspects of using peptide drugs. There are no predictable ways in the art to indicate which peptide drug can be successfully made and used in animals and human. The instant specification also does not provide guidance and/or examples to reasonably correlate the in vitro data (i.e. cell data) to in vivo usage (i.e. usage in human and animals). Thus, undue experimentation would be required to make and use the instant claimed invention in its full scope.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Duflot and Gluck

11. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duflot et al (US 4,499,080; 2/12/1985; cited in the previous Office action 5/3/05), in view of Gluck et al (US 6,040,167; 3/21/2000; priority date 11/2/1992 or earlier; cited previously). The previous rejection over claim 42 is maintained for the reasons of record as set forth in the previous Office action as

well as the reasons below. The previous rejection over claim 57 is moot due to applicant's cancellation of the said claims.

Duflot et al, throughout the patent, teach pharmaceutical compositions comprising conjugates of ST receptor binding moiety (i.e., see claims 1-34) and an agent (toxin) (i.e., see claims 21-34), which reads on the pharmaceutical composition of **clm 42**. The 2nd peptide in Claim 18 or the cytotoxin of Claim 31 of the reference would read on the "radiostable active agent" of **clm 42** because the instant specification defines the term "radiostable" as compounds which are not radioactive at p. 7, para 4. In addition, the instant specification broadly defines the term "therapeutic agent" as "chemotherapeutics, toxins, radiotherapeutics, targeting agents or radiosensitizing agents" at p.7, lines 15+; the instant specification broadly defines the term "imaging agent" as "compounds which can be detected" at p.8, lines 12+. Thus, at least the "cytotoxin" of the reference reads on the "toxins" encompassed by the term "therapeutic agent" or the "imaging agent" (because the cytotoxin can be "detected") as defined by the instant specification.

The reference also teaches buffers in which the said conjugates are contained for immunization (col. 15, lines 50+), and pharmaceutical compositions (e.g. Claim 33 of the reference), which reads on the pharmaceutical carrier or diluent of **clm 42**. The reference discloses ST receptor binding peptides comprising 18 amino acids of sequence Asn-Thr-Phe-Tyr-Cys-Cys-Glu-Leu-Cys-Cys-A-Pro-Ala-Cys-Ala-Gly-Cys-T, in which A and T each represent Tyr or Asn, and A and T are not the same (i.e., see Abstract or claim 1), which read on the SEQ ID Nos 2 and 3 of the instant claims.

The peptide of the reference (as discussed above) inherently possess the property of binding to ST receptor activated guanylyl cyclase C as recited in **clm 42**, as evidenced by the instant specification (spec. p.13, lines 30+). As the peptide of the reference is structurally the same as the peptide of the instant claims (which the instant specification discloses to possess the property of activating guanylyl cyclase C), the peptide of the reference would have the same property and/or function of activating the same target.

The reference also teaches using the peptide in an injectable formula (e.g. col.16, lines 1+), which reads on the "injectable pharmaceutical composition" of **clm 42**.

Duflot et al do not specifically teach the pharmaceutical composition comprises a liposome.

However, Gluck et al, throughout the patent, teach a similar pharmaceutical composition comprising a liposome vesicle (part (a) of Claim 1 of the reference), a fusion peptide (part (b) of Claim 1), and a protein for binding receptor (part (d) of Claim 1). The reference teaches the benefits or advantages of using liposome vesicles to deliver particular drugs (col. 1, lines 55+). The advantages include facilitating transporting the drug through normally impermeable barriers, and improving drug selectivity and reduction in toxicity, etc. (col. 1, lines 57+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to using liposome vesicles to deliver various drugs.

A person of ordinary skill in the art would have been motivated at the time of the invention to use liposome as part of a pharmaceutical composition that comprise fusion peptides (or conjugates) with active drug agents, because using liposome vesicle to deliver drugs offer many advantages such as high permeability and low toxicity as discussed supra.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because Gluck et al have demonstrated the utilization of liposome vesicle as part of a pharmaceutical composition that comprise peptides, and receptor binding proteins.

Discussion and Answer to Argument

12. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the combination of the Duflot and the Gluck references does not teach the added feature of "activate guanylyl cyclase C" in the instant claim. (Reply, p. 17).

Applicants are respectfully directed to the body of the above rejection for detailed discussion how the cited references render the claimed invention obvious. Briefly, the peptide of the reference (as discussed above) inherently possess the property of binding to ST receptor activated guanylyl cyclase C, as evidenced by the instant specification (spec. p.13, lines 30+) because the peptide of the reference is structurally the same (i.e. the same amino acid sequence) as the peptide of the instant disclosure.

Applicants also seem to assert the Duflot reference "teaches away" from the instant claimed invention. (Reply, p.17, para 7).

However, applicants do not provide sufficient reasoning for this alleged "teaching away". Applicants seem to argue the Duflot reference teaches non-toxin peptide, thus the reference

teaches away. However, the instant claims are not drawn to "toxic" peptide. In addition, the structure of the reference's peptide (as discussed above) appears to structurally the same as the peptide of the instant claims (SEQ ID NOs 2 and 3). Thus, it is not clear how the same peptides can have different properties (i.e. non-toxic vs. toxic).

Duflot, Hussain and Trouet

5. Claims 23, 25-27, 30, 32-34, 42-43, 45-48, 50-56 and 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duflot et al (US Patent 4,499,080; 2/12/1985; cited previously), in view of Hussain et al (EP 0341661; 11/15/1989) and Trouet et al (PNAS. Vol. 79: 626-629; 1982). The previous rejection over claims 23, 25-27, 30, 32-34, 42-43, 45-48, 50-56 and 62-67 is maintained for the reasons of record as set forth in the previous Office action as well as the reasons below. The previous rejection over claims 38, 41, 57 and 58 is moot due to applicant's cancellation of the said claims. The rejection over claim 67 is necessitated by applicant's amendment to the claims.

The instant claims recite a pharmaceutical composition comprising; a) a ST receptor binding ligand selected from the group consisting of: antibodies that bind to ST receptor, antibody fragments that bind to ST receptor and peptides that bind to ST receptor; b) a non-peptide radiostable therapeutic agent; and, c) a pharmaceutical carrier or diluent.

Duflot et al, throughout the patent, teach pharmaceutical compositions comprising conjugates of ST receptor binding moiety (i.e., see claims 1-34) and an agent (toxin) (i.e., see claims 21-34), which reads on the pharmaceutical composition of **clms 23**, **42**, and **48**. The ST

receptor binding peptides of the reference read on the ST receptor binding ligand of **clm 23**. The 2nd peptide in Claim 18 or the cytotoxin of Claims 30 and 31 of the reference read on the "radiostable active agent" that is a therapeutic agent of **clms 42**, **48**, **54**, and **55** because the instant specification defines the term "radiostable" as compounds which are not radioactive at p. 7, para 4. In addition, the instant specification broadly defines the term "therapeutic agent" as "chemotherapeutics, toxins, radiotherapeutics, targeting agents or radiosensitizing agents" at p.7, lines 15+; the instant specification broadly defines the term "imaging agent" as "compounds which can be detected" at p.8, lines 12+. Thus, at least the "cytotoxin" of the reference reads on the "toxins" encompassed by the term "therapeutic agent" or the "imaging agent" (because the cytotoxin can be "detected") as defined by the instant specification.

The reference also teaches buffers in which the said conjugates are contained for immunization (col. 15, lines 50+), and pharmaceutical compositions (e.g. Claim 33 of the reference), which reads on the pharmaceutical carrier or diluent of **clms 23**, **42** and **48**. The "buffers" of the reference are not "conjugated" to either the peptides or the active agent, and thus read on the limitation of "said composition is unconjugated" of **clm 48** as the recitation is reasonably and broadly interpreted. The reference discloses ST receptor binding peptides comprising 18 amino acids of sequence Asn-Thr-Phe-Tyr-Cys-Cys-Glu-Leu-Cys-Cys-A-Pro-Ala-Cys-Ala-Gly-Cys-T, in which A and T each represent Tyr or Asn, and A and T are not the same (i.e., see Abstract or claim 1), which read on the SEQ ID Nos 2 and 3 of the instant **clms 25-27**, **32-34**, **38**, **43**, **45**, **50-52** and **62-66**. The recitation "wherein said fragments and derivatives bind to ST receptor" of the instant claims (e.g. Claim 25) is an inherent property of the claimed peptides or ligands. In addition, the instant claim recites "peptides **having an** amino

acid sequence SEQ ID NO:2…" which recitation does not dictate that the instant peptides consist of only the amino acid sequence of the claimed SEQ ID NOs. The said claim language is open ended, and thus the sequence of the reference reads on the instant claimed peptides.

The Duflot reference also teaches formulating the composition into an injectable composition for administering to mice through injection. (e.g. col.16, lines 50+), which read on the injectable pharmaceutical composition of **clms 41**, **57** and **58**.

The peptide of the reference (as discussed above) inherently possess the property of binding to ST receptor activated guanylyl cyclase C as recited in **clms 23, 42** and **67**, as evidenced by the instant specification (spec. p.13, lines 30+). As the peptide of the reference is structurally the same as the peptide of the instant claims (which the instant specification discloses to possess the property of activating guanylyl cyclase C), the peptide of the reference would have the same property and/or function of activating the same target.

The reference also teaches using the peptide in an injectable formula (e.g. col.16, lines 1+), which reads on the "injectable pharmaceutical composition" of **clm 42**.

Duflot et al do not explicitly teach a pharmaceutical composition comprising a "non-peptide radiostable therapeutic agent" as recited in **clms 23**, **47** and **53**. The Duflot reference does not explicitly teach the therapeutic agent is methotrexate or daunorubicin as recited in **clms 30**, **32**, **43**, **46**, **56**, **63** and **64**.

However, **Hussain** et al, throughout the publication, teach conjugating non-peptide compounds such as aminoboronic acid derivatives to peptides as pharmaceutical compositions. (e.g. pp. 2-3). The reference also teaches the advantages of including a chemical compound to

peptides as pharmaceutical composition such as to "stabilize and improve the delivery of pharmacological active peptides" (e.g. p.3, para 1).

In addition, **Trouet** et al, throughout the publication, teach conjugating drugs such as "duanorubicin" with various proteins, peptides or polypeptides as therapeutic reagents (e.g. Abstract). The reference also teaches the need to associate peptides (or proteins) with therapeutic agents (or drugs) for carrying various drugs (e.g. p.626). The reference also teaches using peptides (or proteins) as carriers for selective targeting of anti-tumor drugs (such as methotrexate). (e.g. p.626, para 1).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make a composition comprising a ST receptor binding ligand (i.e. peptides or proteins) and a non-peptide therapeutic agent.

A person of ordinary skill in the art would have been motivated at the time of the invention to make a pharmaceutical composition comprising a carrier peptide such as a ST receptor ligand and a therapeutic agent such as duanorubicin or aminoboroni acid, because both Hussain et al and Trouet et al teach using peptides or proteins as carrier for drug delivery are routine and known in the art, and both of the references teach the need to use carrier peptides for drug delivery such as increased target selectivity and increased drug stability as discussed above. In addition, all the references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, it would have been obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the predictable result of making a pharmaceutical composition. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.*

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Duflot, Hussain and Trouet references have all demonstrated success generation of compositions comprising both peptides and other agents such as non-peptide agents.

Discussion and Answer to Argument

13. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection with similar argument as the traversal over the rejection under Duflot and Gluck. (Reply, pp.18+).

Applicants are respectfully directed to the above discussion for answer to arguments.

Applicants also traversed the above rejection by attacking each reference alone. (Reply, pp.19+).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants also assert "The instant claims 23 and 42, and the claims dependent there from, specifically require that the peptides which bind to ST do not active GCC, i.e. they are non-toxic." (Reply, p.18, last para).

However, the instant claims recite the peptides "activate guanylyl cyclase C" (assuming the abbreviation "GCC" stands for "guanylyl cyclase C"). It is unclear and confusing what applicants are asserting by the above said statement. In addition, applicants also seem to assert the peptides claimed in the instant claims 23 and 42 are "non-toxic". Applicants also assert the peptides of the Duflot reference are also "non-toxic" (e.g. Reply, p.18, last para). Thus, even by applicants' own statement, the peptides of the reference possess the same property as the instant claimed peptides.

Applicants also seem to argue the cited references do not teach "an therapeutic agent." (Reply, p.19, para 1).

Applicants are respectfully directed to the above rejection for discussion of the therapeutic agent.

Applicants also argue the Hussain reference teaches away because it teaches enhanced absorption through mucosal tissue. (Reply, p.19).

Contrary to applicant's assertion, the Hussain reference not only teaches delivery to mucosal tissue, but also teaches delivery through injections (e.g. p.3, lines 20+). The reference teaches various formulations (including nasal sprays and mucosal patches) can be dissolved in

solution for injections (e.g. p.3, lines 20+). Thus, the reference does not teach away from making injectable formulations.

Applicants argue "It is impermissible to use Applicant's own disclosure in a finding of obviousness". (Reply, pp.19-20).

Contrary to applicant's assertion, the above obviousness rejection was not based on applicant's own disclosure. Applicants are respectfully directed to the above rejection for rationales (based on the teachings of the cited references) to combine the cited references.

Duflot and Others

6. Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duflot et al (US Patent 4,499,080; 2/12/1985; cited previously), in view of Hussain et al (EP 0341661; 11/15/1989) and Trouet et al (PNAS. Vol. 79: 626-629; 1982), as applied to claims 23, 25-27, 30, 32-34, 42-43, 45-48, 50-56 and 62-67 above, and further in view of Lee et al (US 5,183,805; 2/2/1993). The previous rejection over claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-66 is maintained for the reasons of record as set forth in the previous Office action as well as the reasons below. The previous rejection over claims 38, 41, 57 and 58 is moot due to applicant's cancellation of the said claims. The rejection over claim 67 is necessitated by applicant's amendment to the claims.

The instant claims recite a pharmaceutical composition comprising; a) a ST receptor binding ligand selected from the group consisting of: antibodies that bind to ST receptor,

antibody fragments that bind to ST receptor and peptides that bind to ST receptor; b) a non-peptide radiostable therapeutic agent; and, c) a pharmaceutical carrier or diluent.

Duflot et al, throughout the patent, teach pharmaceutical compositions comprising conjugates of ST receptor binding moiety and another agent as discussed supra.

Hussain et al, throughout the publication, teach conjugating non-peptide compounds such as aminoboronic acid derivatives to peptides as pharmaceutical compositions as discussed supra. The reference also teaches the advantages of including a chemical compound to peptides as pharmaceutical composition such as to "stabilize and improve the delivery of pharmacological active peptides" (e.g. p.3, para 1).

Trouet et al, throughout the publication, teach conjugating drugs such as "duanorubicin" with various proteins, peptides or polypeptides as therapeutic reagents as discussed supra. The reference also teaches the need to associate peptides (or proteins) with therapeutic agents (or drugs) for carrying various drugs (e.g. p.626). The reference also teaches using peptides (or proteins) as carriers for selective targeting of anti-tumor drugs (such as methotrexate). (e.g. p.626, para 1).

The combination of the Duflot, Hussain and Trouet references does not explicitly teach a pharmaceutical composition comprising 5-fluorouracil as recited in **claims 31**, **36**, **39**, **40** and **44**.

However, Lee et al, throughout the patent, teach compositions comprising peptides and other compounds for cancer therapeutic applications (see Abstract). The reference particularly teaches conjugating peptides (such as EGF peptides) with chemotherapeutic agents including 5-fluorouracil (e.g. col.15, lines 20+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make a composition comprising a ST receptor binding ligand (i.e. peptides or proteins) and a chemotherapeutic drug such as 5-fluorouracil.

A person of ordinary skill in the art would have been motivated at the time of the invention to make a pharmaceutical composition comprising a carrier peptide such as a ST receptor ligand and a therapeutic agent such as 5-fluorouracil, because Lee et al teach the advantages of combining different drugs for synergistic effects such as enhanced drug delivery to specific tumor cells (e.g. col.15, lines 20+). In addition, all the above cited references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, it would have been obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the predictable result of making a pharmaceutical composition for effective drug delivery. See *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396*.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Duflot, Hussain, Trouet and Lee references have all demonstrated success generation of compositions comprising both peptides and other agents such as non-peptide agents.

Discussion and Answer to Argument

14. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection with similar argument as the traversal over the the above rejections. (Reply, pp.20+).

Applicants are respectfully directed to the above discussion for answer to arguments.

Applicants again asserting the above obviousness rejection is based on Applicant's own disclosure. (Reply, pp.20-21).

Contrary to applicant's assertion, the above obviousness rejection was not based on applicant's own disclosure. Applicants are respectfully directed to the above rejection for rationales (based on the teachings of the cited references) to combine the cited references.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5,962,220

16. Claims 23, 25-28, 33, 34, 38, and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, and 6 of U.S. Patent No. 5,962,220 (cited in the previous Office action 5/3/05). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 9/6/06, at pp. 19+.

6,087,109

18. Claims 23, 25-28, 33, 34, 38, and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 and 13 of U.S. Patent No. 6,087,109 (Claims 5 and 1 of the '220 patent). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 9/6/06, at pp. 19+.

7,097,839

19. Claims 23 and 28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24, 26, 28, 29 and 33-41 of U.S. Patent No. 7,097,839. The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 9/6/06, at pp. 19+.

5,962,220 and 6,040,167

20. Claims 23, 25-28, 33, 34, 38, 40, 41, 42, 45, and 47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, 10, and 12 of U.S. Patent No. 5,962,220 in view of Gluck et al (US 6,040,167; 3/21/2000; priority

date 11/2/1992 or earlier; cited previously). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 9/6/06, at pp. 19+.

'901

7. Claims 23, 25-27, 48, 50, 51, 52, 54 and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 12 and 15-17 and 20-22 of copending Application No. 11/494,901 (US 20060269477). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention in the '901 application reads on the instant claimed invention.

The '901 application claims a pharmaceutical composition comprising "a pharmaceutical acceptable carrier…", "a ST receptor binding moiety," and "an active moiety", wherein the active moiety is a therapeutic agent as recited in claims 10 and 12 of the '901 application. The '901 application also recites the same SEQ ID Nos as the ones listed in the instant claims. Because the pharmaceutical carrier is "unconjugated" from the compounds, the claimed invention as recited in claims 10 and 12 of the '901 application read on the composition of the instant claim 48. The '901 application also claims methods of treating using a pharmaceutical composition comprising "a carrier", "a ST receptor ligand", and "a nucleic acid molecule" as recited in claim 22, which composition reads on the instant claimed invention as recited in claim 23.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion and Answer to Argument

21. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants state applicant will file appropriate terminal disclaimers upon indication that the pending claims would be otherwise allowable for the following patents:

5,962,220; 6,087,109; 7,097,839. (Reply, p.21+)

However, the instant claims have not been indicated as allowable, and applicants have not filed the appropriate terminal disclaims to overcome the above rejections. Thus, the said rejections are maintained for the reasons of record.

Applicants also state the provisional double patenting rejection requires no action at this time. (Reply, p.22).

However, the instant claims are not otherwise allowable, thus the said claim rejection is maintained for the reasons of record.

New Claim Objection(s) or Rejection(s)

Claim Objections

22. Claim 67 is objected to because of the following informalities: Claim 67 recites "a peptide that peptides" in line 2 of the claim, which is redundant. Appropriate correction is required.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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AU 1639
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/Jon D. Epperson/
Primary Examiner, AU 1639